A way forward for research on biomarkers for psychiatric disorders

Patricia Boksa, PhD

Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Montréal, Que.

Webster's *New World Medical Dictionary* provides a simple definition of a biomarker as "a biologic feature that can be used to measure the presence or progress of disease or the effects of treatment." In the research literature, the term "candidate biomarker" is often loosely applied to any biological feature associated with a disorder. The search for biomarkers for psychiatric disorders has a long history, with earlier studies investigating molecular markers, like platelet imipramine binding or cerebrospinal 5-hydroxyindoleacetic acid (5-HIAA) in people with depression, or behavioural markers, such as smooth pursuit eye movements in people with schizophrenia. More recent searches continue to look for blood biomarkers (e.g., brain-derived neurotrophic factor and cytokines in people with schizophrenia or depression) and behavioural biomarkers (e.g., fear extinction in people with anxiety), and are progressing on to more high-tech searches, such as the use of proteomics to define signatures of proteins altered in blood or the use of support vector machine analysis to define informative neuroimaging patterns or panels of immunoassays altered in specific disorders.

Biomarker research

One major goal of biomarker research, simply put, is to improve the accuracy of diagnosis to, in turn, improve patient outcomes. This approach has been successful for some disorders, but for psychiatric disorders it poses particular challenges. Identification of a valid biomarker is based on observations that the biomarker is detected in patients with a specific psychiatric disorder and not in healthy controls. However, the fundamental definition of a psychiatric disorder is based on subjective (distress) and/or behavioural (dysfunction) criteria, which are determined clinically. Therefore it is difficult to see how diagnosis and treatment can be improved by simply trying to use a biomarker to help decide whether a person does or does not have a disorder. For example, if a patient has clinical symptoms of obsessive–compulsive disorder (OCD) but lacks a positive biomarker, treatment would still be given. Conversely, if a patient doesn't have enough symptoms of OCD to warrant diagnosis, he will not likely be given treatment even if he has a positive biomarker.

More refined use of biomarkers might be beneficial, for example, if a biomarker could predict the presence of an early disorder that is not yet clinically evident but would show improved outcome with early treatment. In Alzheimer disease, understanding of the temporal ordering of biomarker expression has allowed the field to progress toward incorporating cerebrospinal fluid (CSF) and neuroimaging biomarkers into the diagnostic criteria for detecting early latent disease and for staging and describing disease progression.[1] In addition, a biomarker could prove useful if it could discern between closely related disorders or demarcate subcategories of a disorder and if this categorization resulted in different treatments and outcomes. Taking this notion even further, Kapur and colleagues[2] envision a situation where clusterings of positive biomarkers drive the definition of homogeneous disorder subtypes that may cut across traditional boundaries of DSM-defined disorders.

Examining the evolution of biomarkers for nonpsychiatric disorders may also highlight the special difficulties challenging their use for psychiatric disorders. As an example, consider the use of bone density measurements in the diagnosis and treatment of osteoporosis. A major difference in the situation between psychiatric and nonpsychiatric disorders is that, in the case of nonpsychiatric disorders like osteoporosis, the pathophysiology may be better understood, and there is strong reason to believe that the biomarker is a component in the causation of the disorder and that changes in the biomarkers will reflect outcome. Yet even for osteoporosis, bone density was accorded much more weight as a diagnostic prognosticator until later studies emerged showing that most bone fractures (the major outcome of importance) occur in people with normal or low–normal bone density. Now bone

Correspondence to: P. Boksa, Douglas Institute — Research, Pavilion Perry, Rm. E-2110, 6875 LaSalle Blvd., Verdun QC H4H 1R3; patricia.boksa@mcgill.ca

J Psychiatry Neurosci 2013;38(2):75-7.

DOI: 10.1503/jpn.130018

density is considered to be only 1 of a battery of indicators that can be incorporated into an assessment tool to predict risk.[3]

Compared with some nonpsychiatric disorders, our understanding of the pathophysiology of most psychiatric disorders is scant. The search for biomarkers for Alzheimer disease may be somewhat advanced compared with that for other psychiatric disorders owing in part to an understanding of components of the pathophysiology of Alzheimer disease (amyloid deposition, tau proteinopathy, neuronal degeneration) and their relationship to disease progression and clinical symptoms.[1] For most other psychiatric disorders, even if markers, such as levels of a CSF protein or abnormal neuroimaging findings, are found to be associated with the disorder, it remains largely speculative how these markers relate to the symptoms and pathophysiology of the disorder. Most importantly, for psychiatric disorders, we do not yet have evidence that assessing the profile of a biomarker will alter the clinical outcome of the patient. As an aside, it appears that some recent court cases have already begun to use markers, such as neuroimaging findings and genetic polymorphisms, as arguments to convince the court that the accused has a mitigating psychiatric disorder (clearly affecting the defendant's outcome!).[4] This seems premature given our limited understanding of how these markers relate to the expression of psychiatric symptoms.

Confounding factors

While some candidate biomarkers can be shown to be highly associated with a psychiatric disorder (i.e., high sensitivity), the specificity of the biomarkers for the disorder may also be particularly problematic in the case of psychiatric disorders. In general, there is large overlap in pathophysiological findings among psychiatric disorders, and a biomarker must not only differentiate disorder A from healthy control conditions, but must also differentiate disorder A from disorders B–Z. For example, Benson and colleagues[5] recently described a set of eye movement abnormalities detected using simple viewing tasks that could distinguish people with schizophrenia from healthy controls with 98% accuracy. Yet eye movements are complex functions regulated by multiple brain regions, so one might expect that abnormalities in many brain areas could give rise to disorganized scanning. In fact, scanpath abnormalities are found in many other disorders, so a specific signature of deficits would need to be found that differentiate schizophrenia from other types of psychiatric and neurologic disorders. A factor confounding the utility of many potential biomarkers (e.g., oxidative stress, inflammation, growth factors, prepulse inhibition of startle, altered hypothalamic pituitary adrenal function, neuroimaging disturbances in the default mode network) is that they are found to be altered in multiple psychiatric and neurologic disorders. Some markers may also be readily influenced by environmental and lifestyle factors, such as diet, stress, activity levels and substance abuse, which further confound findings. Of course, confounding effects of psychotropic medications on biomarker findings remain an ongoing issue.

Approaches to biomarkers for psychiatric disorders

Given the lack of specificity of many biological findings in psychiatry and the very nature of psychiatric disorders, which are multifactorial in etiology and heterogeneous in expression, it is unlikely that any 1 biomarker will greatly impact diagnosis and treatment. Progress in biomarker research for psychiatric disorders will almost certainly require a more complex approach incorporating a range of biological findings that have been associated with a particular disorder. Several groups are working on incorporating a multiplicity of clinical, socio-environmental, molecular, neuroimaging and neurophysiological findings associated with a psychiatric disorder (e.g., Alzheimer disease,[6] depressive disorder,[7,8] schizophrenia[9]) to detect particular signatures of the disorder. The identification of the relevant biomarkers in these approaches may be based on either a theoretical framework derived from existing evidence about the disorder[7] or on an atheoretical informatics approach that does not rely on understanding mechanisms.[8]

One of the most advanced projects in this respect is the Alzheimer's Disease Neuroimaging Initiative. Funded jointly by the U.S. National Institutes of Health, the pharmaceutical industry and other organizations since 2004, it initially involved researchers in more than 50 American and Canadian sites collecting longitudinal imaging, genetic, biochemical and clinical data in a standardized way on a large population at high risk for or with Alzheimer disease, and is now being extended to include collection of data from countries around the world.[6] Remarkably, this huge data set is freely available to any researcher wishing to investigate or confirm their individual findings and hypotheses. An expected benefit from this approach is the use of biomarker signatures to define the members of current high-risk populations in whom Alzheimer disease is most likely to develop, thus decreasing the numbers of participants needed and the costs for clinical drug trials. In a similar vein, a Canadian multicentre initiative to define biological signatures for subpopulations of major depressive disorder, derived from a wide range of clinical, genetic, neuroimaging and biochemical markers, is also currently underway.[8]

While such intensive approaches will not be practical to assess individual patients in daily clinical practice, it is hoped that a workable small number of key informative biomarkers will emerge. This seems to be the way the field is headed, but there appears to be much work ahead to analyze large data sets of patient characteristics and biomarkers to discover biomarker signatures that define patient subgroups and to experimentally validate whether these signatures predict treatment response. A further hurdle will be to determine whether one can tailor a biomarker signature approach that is practically and economically viable for clinical practice. For this to happen, meaningful differences in treatment response will need to be achieved using a small, workable number of biomarkers. In addition, the major problem of standardization of biomarkers in a clinical setting (e.g., quantification of neuroimaging measurements) will need to

be addressed.[1] The practical establishment of biomarker availability will also open a variety of ethical and social issues related to their use, as discussed in a recent commentary.[10] In the final analysis, the major challenge for biomarker research will be to demonstrate that it provides improved outcomes compared with current clinical diagnosis.

Competing interests: None declared.

References

1. Jack CR Jr. Alzheimer disease: new concepts on its neurobiology and the clinical role imaging will play. *Radiology* 2012;263:344-61.
2. Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Mol Psychiatry* 2012;17:1174-9.
3. Baim S, Leslie WD. Assessment of fracture risk. *Curr Osteoporos Rep* 2012;10:28-41.
4. Feresin E. Italian court reduces murder sentence based on neuroimaging data. In: *Nature News Blog* [a website of nature.com]. 2011 Sept. 1. Available: http://blogs.nature.com/news/2011/09/italian_court_reduces_murder_s.html (accessed 2013 Jan. 7).
5. Benson PJ, Beedie SA, Shephard E, et al. Simple viewing tests can detect eye movement abnormalities that distinguish schizophrenia cases from controls with exceptional accuracy. *Biol Psychiatry* 2012; 72:716-24.
6. Burton A. Big science for a big problem: ADNI enters its second phase. *Lancet Neurol* 2011;10:206-7.
7. Kemp AH, Gordon E, Rush AJ, et al. Improving the prediction of treatment response in depression: integration of clinical, cognitive, psychophysiological, neuroimaging, and genetic measures. *CNS Spectr* 2008;13:1066-86.
8. Kennedy SH, Downar J, Evans KR, et al. The Canadian Biomarker Integration Network in Depression (CAN-BIND): advances in response prediction. *Curr Pharm Des* 2012;18:5976-89.
9. Shah J, Eack SM, Montrose DM, et al. Multivariate prediction of emerging psychosis in adolescents at high risk for schizophrenia. *Schizophr Res* 2012;141:189-96.
10. Singh I, Rose N. Biomarkers in psychiatry. *Nature* 2009;460:202-7.

JPN's top articles*

1. **How to increase serotonin in the human brain without drugs**
   Young
   J Psychiatry Neurosci 2007;32(6):394–99
2. ***N*-acetylcysteine in psychiatry: current therapeutic evidence and potential mechanisms of action**
   Dean et al.
   J Psychiatry Neurosci 2011;36(2):78–86
3. **L-Tyrosine to alleviate the effects of stress?**
   Young
   J Psychiatry Neurosci 2007;32(3):224
4. **Are SAMe and 5-HTP safe and effective treatments for depression?**
   Young
   J Psychiatry Neurosci 2003;28(6):471
5. **The role of GABAA receptors in mediating the effects of alcohol in the central nervous system**
   Davies
   J Psychiatry Neurosci 2003;28(4):263–74
6. **What exactly is a mood stabilizer?**
   Young
   J Psychiatry Neurosci 2004;29(2):87–8
7. **What is the best treatment for bipolar depression?**
   Young
   J Psychiatry Neurosci 2008;33(6):487–8
8. **Stressed or stressed out: What is the difference?**
   McEwen
   J Psychiatry Neurosci 2005;30(5):315–18
9. **The long-term impact of treatment with electroconvulsive therapy on discrete memory systems in patients with bipolar disorder**
   MacQueen et al.
   J Psychiatry Neurosci 2007;32(4):241–9
10. **Universities, governments and industry: Can the essential nature of universities survive the drive to commercialize?**
    Young
    J Psychiatry Neurosci 2005;30(3):160–3

*Based on page views on PubMed Central.
Updated February 12, 2013.